Should children with esophageal varices receive beta-blockers for the primary prevention of variceal hemorrhage?

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Esophageal variceal hemorrhage occurs in up to 10% of children with portal hypertension annually, and may be fatal. In contrast to the strong evidence in adults that nonselective beta-adrenergic antagonism reduces the risk of variceal bleeding by approximately 50%, few pediatric data are available. The use of beta-blockers for primary prophylaxis has been reported in children, but not tested in a randomized controlled trial. The risks and benefits in children remain unquantified and may differ from adults in light of the different cardiovascular response to hypovolemia in young children. The circumstances of the individual patient must, therefore, be carefully considered before beta-blockers are prescribed to children with esophageal varices.

Key Words: *Adrenergic beta-antagonists; Children; Esophageal and gastric varices; Hypertension, portal; Propranolol*

Variceal hemorrhage is a life-threatening complication of portal hypertension that occurs commonly in children with chronic liver disease or portal vein obstruction (1-8). In children with biliary atresia, the incidence of variceal hemorrhage ranges from 17% to 29% over a five- to 10-year period (3-5) and is 50% in children who survive more than 10 years without liver transplantation (6). Among 50 children with esophageal varices, primarily due to cirrhosis, who were prospectively followed and not offered active treatment to prevent variceal bleeding, 42% suffered upper gastrointestinal hemorrhage during a median 4.5 year follow-up period (2). For children with portal vein thrombosis, the available studies suggest that up to 50% suffer a major variceal hemorrhage by 16 years of age (1). The mortality rate from gastrointestinal bleeding ranges from 2.5% to 20% in children with portal hypertension (2,4,7,8). Prevention is, therefore, an important goal.

Although the majority of North American pediatric hepatologists report a willingness to use beta-blockers for primary prophylaxis (9), this approach in children is controversial due to the lack of pediatric data and the wariness among pediatricians of extrapolating results of adult studies to children (10). The present review discusses the mechanism of action of beta-blockers in the context of the pathophysiology of portal hypertension, compares the evidence for pharmacological and endoscopic prophylaxis in both adults and children, and considers the additional factors that determine whether nonselective beta blockade is an appropriate intervention for children at risk of variceal hemorrhage.

Les enfants présentant des varices œsophagiennes devraient-ils recevoir des bêta-bloquants en prévention primaire des hémorragies variqueuses?

L'hémorragie œsophagienne variqueuse s'observe chez jusqu'à 10 % des enfants qui souffrent d'hypertension portale chaque année et elle peut être fatale. Contrairement aux preuves solides enregistrées chez les adultes à l'effet que l'antagonisme bêta-adrénergique non sélectif réduit le risque d'hémorragie variqueuse d'environ 50 %, on dispose de peu de données à cet égard chez les enfants. L'utilisation des bêta-bloquants en prophylaxie primaire a été signalée chez les enfants, mais n'a pas été mise à l'épreuve dans le cadre d'essais contrôlés randomisés. Les risques et les avantages chez les enfants n'ont pas été mesurés et pourraient différer de ce qui s'observe chez les adultes, puisque la réponse cardiovasculaire à l'hypovolémie est différente chez les jeunes enfants. Les conditions propres à chaque patient doivent donc, par conséquent, être étudiées avec soin avant que l'on ne prescrive des bêta-bloquants à des enfants qui présentent des varices œsophagiennes.

THE PATHOPHYSIOLOGY OF PORTAL HYPERTENSION AND THE MECHANISM OF ACTION OF NONSELECTIVE BETA-BLOCKERS

In portal hypertension caused by cirrhotic liver disease, vascular resistance in the portal system is elevated by distorted hepatic architecture, intrahepatic small vessel thromboses and increased intrahepatic vascular tone arising from the actions of vasoactive substances on myofibroblasts, perisinusoidal activated stellate cells and vascular smooth muscle cells (11-16). Whereas the intrahepatic vascular bed is constricted, splanchnic arteriolar dilation exacerbates portal hypertension by increasing portal venous inflow (17-19).

Varices develop when the hepatic venous pressure gradient (HVPG), a measurement obtained by transjugular cannulation of the hepatic veins (20), is elevated above 10 mmHg to 12 mmHg (21). Recent evidence suggests that active angiogenesis may contribute to the development of varices in addition to the effect of increased pressure and flow within potential portosystemic anastomoses (22). Variceal bleeding occurs when increased vein diameter, decreased wall thickness and increased intraluminal pressure elevate variceal wall tension beyond the maximum tolerable threshold (19). Clinical predictors of variceal hemorrhage in adults include the severity of liver disease measured by the Child-Pugh score, the presence of ascites, the size and appearance of the varices at endoscopy, as well as the degree of elevation of HVPG (23).

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TABLE 1
Studies reporting the use of therapies to prevent the first variceal hemorrhage in children

	n	Study details	Controls	Follow-up	Esophageal variceal bleeding (%)
Beta-blockers					
Shashidhar et al (45)	17	Case series, four further children received secondary prophylaxis, results provided reflect outcome in all 21 children. Two children had prehepatic PHT. All-cause upper GI bleeding in seven children (33%).	None	3 years	24
Ozsoylu et al (46)	45	Case series, all with biopsy-proven cirrhosis.	None	5.5 years	16
Erkan et al (47)	13	Case series, three with prehepatic PHT. Additional seven patients treated with combined beta-blocker and EIS, one with bleeding.	None	5.2 years	15
Endoscopic variceal ligation					
Sasaki et al (80)	9	Case series, all with biliary atresia. Only early outcome reported, appearance of varices improved or eradicated in six, not improved in three after one to seven sessions of ligation with loop-ligator.	None	7–14 days	0
Celinska-Cedro et al (78)	31	Case series, 50% prehepatic PHT. One child had bleeding from portal gastropathy.	None	1.3 years	0
Cano et al (77)	4	Case series, 50% with prehepatic PHT.	None	Not given	0
EIS					
Howard et al (91)	17	Case series, one child with prehepatic PHT.	None	2.5 years	0
Maksoud et al (92)	26	Case series, approximately 27% prehepatic. Two died with variceal bleeding during follow-up.	None	1.9 years	42
Gonçalves et al (2)	100	Randomized controlled trial, 50 children underwent EIS versus 50 controls, 9% with prehepatic PHT. Results for any cause of upper GI bleeding, 24% EIS versus 48% controls, $P<0.05$.	n=50, no therapy	4.5 years	6 EIS versus 42 controls ($P<0.05$)

EIS Endoscopic injection sclerotherapy; GI Gastrointestinal; PHT Portal hypertension

Nonselective beta-blockers reduce the HVPG by reduction of cardiac output (mediated by beta-1-receptor antagonism), reduction of portal venous flow by unopposed alpha-receptor-mediated splanchnic vasoconstriction (following antagonism of beta-2-receptors) and by antagonism of the noradrenaline-induced constriction of intrahepatic myofibroblasts, activated stellate cells and vascular smooth muscle cells (12,13,24-26).

STUDIES OF BETA-BLOCKERS IN CHILDREN WITH PORTAL HYPERTENSION

Following early reports of potential benefit more than 20 years ago (27,28), nonselective beta-blockers were shown to be superior to placebo or no active treatment in the prevention of first variceal hemorrhage in several randomized controlled trials in cirrhotic adults (29-37). Meta-analyses of these studies confirm that beta-blockers reduce the incidence of variceal hemorrhage by approximately 50% (38-40).

However, in light of numerous examples of drugs whose efficacy, pharmacokinetics or adverse event profiles differ significantly between adults and children, care must be taken before extrapolating to children the evidence for efficacy of beta-blockers in cirrhotic adults (41,42). Biliary atresia is the most common cause of advanced liver disease in children and largely accounts for the excess of biliary disease among cirrhotic children, whereas alcoholic liver disease accounted for the majority of the adults included in the randomized studies of beta-blocker prophylaxis. Although there is no difference in response to beta-blocker prophylaxis between alcoholic and other cirrhotic adults (30-33,36,43), it is difficult to estimate whether a one-year-old infant with biliary atresia will respond to beta-blockers similarly to a 60-year-old adult with alcoholic cirrhosis. Pediatric data are, therefore, needed.

The ability of propranolol to reduce portal pressure was initially studied in 13 children with portal hypertension who received 2.1 mg/kg/day to 8.0 mg/kg/day of propranolol that

induced an average decrease in heart rate of 25% of baseline (44). Four children with decompensated cirrhosis showed little or no response, and overall, the splenic pulp pressure (a proxy for portal venous pressure) decreased by a mean of only 13%, from 387 mmH₂O to 337 mmH₂O. This suggests a limited efficacy of propranolol in these children, although the value of this measurement in predicting variceal hemorrhage is untested.

Clinical experience with propranolol was reported in a retrospective uncontrolled study from Boston, USA, which included a mixed group of 21 children: 19 children had cirrhosis, two had extrahepatic portal vein obstruction, 17 children received primary prophylaxis and four received secondary prophylaxis (45). The propranolol dosage schedule aimed to reduce the heart rate by 25% (achieved in 17 children). Seven of 21 children (33%) had upper gastrointestinal hemorrhage during a median follow-up period of three years. All adverse events (including rash, dizziness, bradycardia, hypotension and depression) were classified as mild and transient, and none required discontinuation of therapy (45).

Additional uncontrolled retrospective studies of propranolol usage in children with portal hypertension have been reported from Turkey. Seven of 45 children (15.6%) and one of 10 children (10%) with cirrhosis, who were not screened for varices, suffered upper gastrointestinal hemorrhage while receiving propranolol for primary prophylaxis during a median five years of follow-up in two studies from different Turkish centres (46,47). Bleeding was less common in children with Child's class A cirrhosis (7.1%) than in those with Child's class B and C combined (29.4%) (46). The incidence of adverse effects was not reported.

Overall, the proportion of children that bled in these studies ranged from 2% to 11% per year of follow-up; no data from untreated control groups are provided (Table 1). In the studies of the natural history of portal hypertension in children that are summarized above, between 2% and 9% of children who

did not receive prophylactic treatment suffered gastrointestinal hemorrhage during each year of follow-up. The efficacy of nonselective beta-blockers for the prevention of variceal bleeding in children, therefore, remains unclear, and the adverse event profile associated with this indication has yet to be adequately defined.

POTENTIAL FOR HARM: REPORTED AND THEORETICAL RISKS OF BETA-BLOCKERS IN CHILDREN WITH PORTAL HYPERTENSION

Children who receive nonselective beta-blockers may develop adverse effects, including bradycardia, heart failure, hypotension, conduction disorders, bronchospasm and hypoglycemia following fasting. However, these drugs are generally well tolerated; no clinically significant adverse events were reported in nine randomized controlled trials that included 309 children of whom 188 received propranolol for indications other than the prevention of variceal hemorrhage (48-56). Although there is no excess mortality among adults who bleed while receiving prophylaxis (29-40), young children respond differently to shock by relying more heavily on tachycardia due to their relatively fixed stroke volume (57). There is an important theoretical concern that, by limiting tachycardia, nonselective beta-blockers may impair tolerance of hypovolemia and worsen the outcome from variceal hemorrhage. There appear to be no reports that suggest increased morbidity or mortality following hemorrhage in children receiving appropriate therapeutic doses of nonselective beta-blockers, although the large controlled studies required to show such an effect have not been undertaken.

HOW MUCH BETA-BLOCKER?

If beta-blockers are to be used in children with portal hypertension, an effective and safe dosing regimen must be chosen. Heart rate is the most commonly used clinical end point for dosage regulation of beta-blockers in the prevention of variceal hemorrhage in adults. In most studies, the beta-blocker dose is adjusted until the heart rate is reduced to 75% of its baseline value, an arbitrary threshold chosen by Lebrech et al (27) in their original study. However, there is only a weak correlation between the effects of nonselective beta blockade on heart rate and portal hemodynamics, and variceal hemorrhage occurs in some cirrhotic adults taking beta-blockers in spite of an adequate heart rate response (44,58,59). The routine use of HVPG measurements improves the prediction of response to beta-blocker therapy; a decline in HVPG to less than 12 mmHg, or by more than 20% of its baseline value, predicts a significantly lower risk of hemorrhage (0% to 7% incidence) compared with patients who fail to achieve this reduction in HVPG (33% to 41% incidence) (60-62). The place for routine clinical use of this relatively invasive but reportedly safe test is the subject of much debate and has yet to be tested in prospective trials (63-66).

While such studies are awaited, common clinical practice among adult hepatologists is to prescribe enough beta-blocker to reduce the heart rate to 75% of its baseline value. The reported experience of propranolol usage in children with portal hypertension follows a similar strategy, with most children requiring between 1 mg/kg/day and 2 mg/kg/day to achieve the required reduction in heart rate; the risk of bleeding is possibly greater in those receiving less than 1 mg/kg/day (45).

Unfortunately, there are no pediatric data to describe the splanchnic hemodynamic response to beta blockade or the optimum dosage schedule that gives maximum efficacy (in reducing hemorrhage episodes) and minimum risk (especially impaired tolerance of shock).

THERAPEUTIC OPTIONS FOR PROPHYLAXIS OF VARICEAL BLEEDING IN CHILDREN

Endoscopic variceal ligation (EVL) provides an alternative approach to the prevention of variceal bleeding that avoids the need for long-term medication, is often suitable for patients with side effects or contraindications to beta-blockers and is at least as effective as nonselective beta-blockers in cirrhotic adults (67-76).

The evidence supporting endoscopic treatment of varices in children is more limited, although many pediatric gastroenterologists are willing to use this approach for primary prophylaxis (9). The only randomized controlled trial of primary prophylaxis of variceal hemorrhage in children studied the effect of endoscopic injection sclerotherapy (EIS) in 100 children of median age 4.3 years in Brazil (2). Most of the children had biliary atresia or another parenchymal liver disease, while nine had portal vein thrombosis. Statistically significant differences were shown between the EIS group and control group (who received no active treatment) in the all-cause gastrointestinal hemorrhage rate (24% versus 48%, respectively) and the variceal hemorrhage rate (6% versus 42%, respectively) (2). Mortality rates were similar. The study excluded children who had the largest (grade 4) varices, and set no minimum requirement for variceal size, but the hemorrhage rate in the control group was still greater than 40%. The report does not provide details of the method for selection of patients for inclusion in the study or of the timing and method of random assignment, including the process to avoid allocation bias. The interpretation of this study and the application of its results to clinical practice are, therefore, difficult.

EIS proved ineffective for primary prophylaxis in adults and has been largely replaced by EVL. Several uncontrolled case series of EVL in children suggest that it is safe, although there is little experience of its use for primary prophylaxis (77-80) (Table 1). In one series of 31 children with varices who underwent EVL, there were no episodes of variceal hemorrhage and only one incidence of bleeding from portal gastropathy, suggesting that this therapy may offer effective prevention for children with both intrahepatic and prehepatic portal hypertension (78).

As with the pediatric beta-blocker studies, the lack of control groups means that there are inadequate data to base any recommendation concerning the use of an endoscopic approach to primary prophylaxis of variceal hemorrhage in children. For adults, the relative efficacy and practicality of different pharmacological, endoscopic or combined approaches to prevention of hemorrhage is vigorously debated (81-83). However, the use of nonselective beta-blockers is more cost effective than EVL (84,85) and, therefore, beta-blockers remain the most widely recommended first-line prophylaxis for adult patients with varices that are at risk of bleeding (64,86-89).

INDIVIDUAL PATIENT CHARACTERISTICS

It is likely that postpubertal teenagers with portal hypertension respond to beta-blockers and bleeding like adults, whereas the

theoretical concerns about adverse outcomes from hemorrhage while receiving beta-blockers apply primarily to infants and younger children. Age may, therefore, be an important factor in the decision to prescribe beta-blockers.

Children and families differ in their perception and management of anxiety and uncertainty. Some accept endoscopic screening for varices without hesitation and are reassured by documentation of the absence of esophageal varices or are encouraged to make clear emergency action plans if large varices are identified, as well as make more informed decisions about such things as vacation travel or relocation to remote areas. Some may prefer pharmacological prophylaxis to a series of EVL procedures with its attendant need in children for general anesthesia.

In making a decision about a treatment plan for which the evidence is unclear, families will differ in their understanding and interpretation of the information provided to them, in their acceptance of risk and their perception of possible benefits. Most clinicians recognize that these differences among families form an important part of treatment decisions and accept that doctors do not always know what is best for each individual child that they treat; their practice has, therefore,

moved toward fuller discussion with families and facilitation of a greater role for the child and family in the decision-making process (90).

SUMMARY

Nonselective beta-blocker therapy reduces the incidence of first variceal hemorrhage in cirrhotic adults with large varices and is more cost-effective than EVL. Unfortunately, 25 years after the dawn of pharmacological prevention of variceal hemorrhage in adults, there remains a pressing need for randomized controlled studies in children at risk of fatal variceal hemorrhage. Meanwhile, pediatric gastroenterologists who wish to prescribe nonselective beta-blockers for primary prophylaxis must be mindful of the lack of pediatric evidence and the potential age-related adverse effects. They should carefully consider each patient's circumstances and discuss the situation fully with the patient and parents, whose opinions of what is best should be carefully heard.

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REFERENCES

1. Lykavieris P, Gauthier F, Hadchouel P, Duche M, Bernard O. Risk of gastrointestinal bleeding during adolescence and early adulthood in children with portal vein obstruction. *J Pediatr* 2000;136:805-8.
2. Goncalves ME, Cardoso SR, Maksoud JG. Prophylactic sclerotherapy in children with esophageal varices: Long-term results of a controlled prospective randomized trial. *J Pediatr Surg* 2000;35:401-5.
3. Miga D, Sokol RJ, Mackenzie T, Narkewicz MR, Smith D, Karrer FM. Survival after first esophageal variceal hemorrhage in patients with biliary atresia. *J Pediatr* 2001;139:291-6.
4. van Heurn LW, Saing H, Tam PK. Portoenterostomy for biliary atresia: Long-term survival and prognosis after esophageal variceal bleeding. *J Pediatr Surg* 2004;39:6-9.
5. Kobayashi A, Itabashi F, Ohbe Y. Long-term prognosis in biliary atresia after hepatic portoenterostomy: Analysis of 35 patients who survived beyond 5 years of age. *J Pediatr* 1984;105:243-6.
6. Toyosaka A, Okamoto E, Okasora T, Nose K, Tomimoto Y. Outcome of 21 patients with biliary atresia living more than 10 years. *J Pediatr Surg* 1993;28:1498-501.
7. Mitra SK, Kumar V, Datta DV, et al. Extrahepatic portal hypertension: a review of 70 cases. *J Pediatr Surg* 1978;13:51-7.
8. Webb LJ, Sherlock S. The aetiology, presentation and natural history of extra-hepatic portal venous obstruction. *Q J Med* 1979;48:627-39.
9. Shneider BL. Approaches to the management of pediatric portal hypertension: Results of an informal survey. In: Groszmann RJ, Bosch J, eds. *Portal Hypertension in the 21st Century*. Dordrecht, The Netherlands: Kluwer Academic Publishers, 2004:167-72.
10. Schreiber RA. Propranolol and portal hypertension: Should kids be on the block? *J Pediatr Gastroenterol Nutr* 1999;29:10-1.
11. Wanless IR, Wong F, Blendis LM, Greig P, Heathcote EJ, Levy G. Hepatic and portal vein thrombosis in cirrhosis: Possible role in development of parenchymal extinction and portal hypertension. *Hepatology* 1995;21:1238-47.
12. Garcia-Pagan JC, Bosch J, Rodes J. The role of vasoactive mediators in portal hypertension. *Semin Gastrointest Dis* 1995;6:140-7.
13. Ballet F, Chretien Y, Rey C, Poupon R. Differential response of normal and cirrhotic liver to vasoactive agents. A study in the isolated perfused rat liver. *J Pharmacol Exp Ther* 1988;244:283-9.
14. Farzaneh-Far R, Moore K. Cysteinyl-leukotrienes and the liver. *Prostaglandins Other Lipid Mediat* 2003;72:35-50.
15. Kaneda K, Ekataksin W, Sogawa M, Matsumura A, Cho A, Kawada N. Endothelin-1-induced vasoconstriction causes a significant increase in portal pressure of rat liver: localized constrictive effect on the distal segment of preterminal portal venules as revealed by light and electron microscopy and serial reconstruction. *Hepatology* 1998;27:735-47.
16. Kawada N, Tran-Thi TA, Klein H, Decker K. The contraction of hepatic stellate (Ito) cells stimulated with vasoactive substances. Possible involvement of endothelin 1 and nitric oxide in the regulation of the sinusoidal tonus. *Eur J Biochem* 1993;213:815-23.
17. Benoit JN, Zimmerman B, Premen AJ, Go VL, Granger DN. Role of glucagon in splanchnic hyperemia of chronic portal hypertension. *Am J Physiol* 1986;251:G674-7.
18. Wiest R, Groszmann RJ. The paradox of nitric oxide in cirrhosis and portal hypertension: Too much, not enough. *Hepatology* 2002;35:478-91.
19. Bosch J, D'Amico G, Garcia-Pagan JC. Portal hypertension. In: Schiff ER, Sorrell MF, Maddrey WC, eds. *Schiff's Diseases of the Liver*, 9th edn. Philadelphia: Lippincott Williams & Wilkins, 2003:429-85.
20. Groszmann RJ, Wongcharatrawee S. The hepatic venous pressure gradient: Anything worth doing should be done right. *Hepatology* 2004;39:280-2.
21. Garcia-Tsao G, Groszmann RJ, Fisher RL, Conn HO, Atterbury CE, Glickman M. Portal pressure, presence of gastroesophageal varices and variceal bleeding. *Hepatology* 1985;5:419-24.
22. Fernandez M, Vizzutti F, Garcia-Pagan JC, Rodes J, Bosch J. Anti-VEGF receptor-2 monoclonal antibody prevents portal-systemic collateral vessel formation in portal hypertensive mice. *Gastroenterology* 2004;126:886-94.
23. Merkel C, Zoli M, Siringo S, et al. Prognostic indicators of risk for first variceal bleeding in cirrhosis: a multicenter study in 711 patients to validate and improve the North Italian Endoscopic Club (NIEC) index. *Am J Gastroenterol* 2000;95:2915-20.
24. Lebrec D. Pharmacological treatment of portal hypertension: Hemodynamic effects and prevention of bleeding. *Pharmacol Ther* 1994;61:65-107.
25. Westaby D, Bihari DJ, Gimson AE, Crossley IR, Williams R. Selective and non-selective beta receptor blockade in the reduction of portal pressure in patients with cirrhosis and portal hypertension. *Gut* 1984;25:121-4.
26. Lebrec D, Hillon P, Munoz C, Goldfarb G, Nouel O, Benhamou JP. The effect of propranolol on portal hypertension in patients with cirrhosis: A hemodynamic study. *Hepatology* 1982;2:523-7.
27. Lebrec D, Nouel O, Corbic M, Benhamou JP. Propranolol – a medical treatment for portal hypertension? *Lancet* 1980;2:180-2.
28. Lebrec D, Poynard T, Bernuau J, et al. A randomized controlled study of propranolol for prevention of recurrent gastrointestinal bleeding in patients with cirrhosis: A final report. *Hepatology* 1984;4:355-8.

29. Pascal JP, Cales P. Propranolol in the prevention of first upper gastrointestinal tract hemorrhage in patients with cirrhosis of the liver and esophageal varices. *N Engl J Med* 1987;317:856-61.
30. Lebrech D, Poynard T, Capron JP, et al. Nadolol for prophylaxis of gastrointestinal bleeding in patients with cirrhosis. A randomized trial. *J Hepatol* 1988;7:118-25.
31. Ideo G, Bellati G, Fesce E, Grimoldi D. Nadolol can prevent the first gastrointestinal bleeding in cirrhotics: A prospective, randomized study. *Hepatology* 1988;8:6-9.
32. Propranolol prevents first gastrointestinal bleeding in non-ascitic cirrhotic patients. Final report of a multicenter randomized trial. The Italian multicenter project for propranolol in prevention of bleeding. *J Hepatol* 1989;9:75-83.
33. Andreani T, Poupon RE, Balkau BJ, et al. Preventive therapy of first gastrointestinal bleeding in patients with cirrhosis: Results of a controlled trial comparing propranolol, endoscopic sclerotherapy and placebo. *Hepatology* 1990;12:1413-9.
34. Colman J, Jones P, Finch C, Dudley F. Propranolol in the prevention of variceal haemorrhage in alcoholic cirrhotic patients. *Hepatology* 1990;12:851.
35. Conn HO, Grace ND, Bosch J, et al. Propranolol in the prevention of the first hemorrhage from esophagogastric varices: A multicenter, randomized clinical trial. The Boston-New Haven-Barcelona portal hypertension study group. *Hepatology* 1991;13:902-12.
36. Prophylaxis of first hemorrhage from esophageal varices by sclerotherapy, propranolol or both in cirrhotic patients: A randomized multicenter trial. The PROVA study group. *Hepatology* 1991;14:1016-24.
37. Strauss E, de Sa MF, Albano A, Lacet CMC, Leiti MO, Maffei RA Jr. A randomised controlled trial for the prevention of the first upper gastro- intestinal bleeding due to portal hypertension in cirrhosis: Sclerotherapy or propranolol versus control groups. *Hepatology* 1988;8:1395. (Abst)
38. Pagliaro L, D'Amico G, Sorensen TI, et al. Prevention of first bleeding in cirrhosis. A meta-analysis of randomized trials of nonsurgical treatment. *Ann Intern Med* 1992;117:59-70.
39. Hayes PC, Davis JM, Lewis JA, Bouchier IA. Meta-analysis of value of propranolol in prevention of variceal haemorrhage. *Lancet* 1990;336:153-6. (Erratum in 1990;336:324).
40. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: A meta-analytic review. *Hepatology* 1995;22:332-54.
41. Steinbrook R. Testing medications in children. *N Engl J Med* 2002;347:1462-70.
42. Caldwell PH, Murphy SB, Butow PN, Craig JC. Clinical trials in children. *Lancet* 2004;364:803-11.
43. Poynard T, Cales P, Pasta L, et al. Beta-adrenergic-antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices. An analysis of data and prognostic factors in 589 patients from four randomized clinical trials. Franco-Italian multicenter study group. *N Engl J Med* 1991;324:1532-8.
44. Ozsoylu S, Kocak N, Yuce A. Propranolol therapy for portal hypertension in children. *J Pediatr* 1985;106:317-21.
45. Shashidhar H, Langhans N, Grand RJ. Propranolol in prevention of portal hypertensive hemorrhage in children: A pilot study. *J Pediatr Gastroenterol Nutr* 1999;29:12-7.
46. Ozsoylu S, Kocak N, Demir H, Yuce A, Gurakan F, Ozen H. Propranolol for primary and secondary prophylaxis of variceal bleeding in children with cirrhosis. *Turk J Pediatr* 2000;42:31-3.
47. Erkan T, Cullu F, Kutlu T, et al. Management of portal hypertension in children: A retrospective study with long-term follow-up. *Acta Gastroenterol Belg* 2003;66:213-7.
48. Aarsland A, Chinkes D, Wolfe RR, et al. Beta-blockade lowers peripheral lipolysis in burn patients receiving growth hormone. Rate of hepatic very low density lipoprotein triglyceride secretion remains unchanged. *Ann Surg* 1996;223:777-87.
49. Olness K, MacDonald JT, Uden DL. Comparison of self-hypnosis and propranolol in the treatment of juvenile classic migraine. *Pediatrics* 1987;79:593-7.
50. Buchhorn R, Hulpke-Wette M, Hilgers R, Bartmus D, Wessel A, Bursch J. Propranolol treatment of congestive heart failure in infants with congenital heart disease: The CHF-PRO-INFANT trial. Congestive heart failure in infants treated with propranolol. *Int J Cardiol* 2001;79:167-73.
51. Gidding SS, Rocchini AP, Beekman R, et al. Therapeutic effect of propranolol on paradoxical hypertension after repair of coarctation of the aorta. *N Engl J Med* 1985;312:1224-8.
52. Leenen FH, Balfe JA, Pelech AN, Barker GA, Balfe JW, Olley PM. Postoperative hypertension after repair of coarctation of aorta in children: Protective effect of propranolol? *Am Heart J* 1987;113:1164-73.
53. Hart DW, Wolf SE, Chinkes DL, Lal SO, Ramzy PI, Herndon DN. Beta-blockade and growth hormone after burn. *Ann Surg* 2002;236:450-6.
54. Herndon DN, Hart DW, Wolf SE, Chinkes DL, Wolfe RR. Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med* 2001;345:1223-9.
55. Herndon DN, Dasu MR, Wolfe RR, Barrow RE. Gene expression profiles and protein balance in skeletal muscle of burned children after beta-adrenergic blockade. *Am J Physiol Endocrinol Metab* 2003;285:E783-9.
56. Berenson GS, Shear CL, Chiang YK, Webber LS, Voors AW. Combined low-dose medication and primary intervention over a 30-month period for sustained high blood pressure in childhood. *Am J Med Sci* 1990;299:79-86.
57. Witte MK, Hill JH, Blumer JL. Shock in the pediatric patient. *Adv Pediatr* 1987;34:139-73.
58. Bosch J, Masti R, Kravetz D, et al. Effects of propranolol on azygos venous blood flow and hepatic and systemic hemodynamics in cirrhosis. *Hepatology* 1984;4:1200-5.
59. Garcia-Tsao G, Grace ND, Groszmann RJ, et al. Short-term effects of propranolol on portal venous pressure. *Hepatology* 1986;6:101-6.
60. Bureau C, Peron JM, Alric L, et al. "A la carte" treatment of portal hypertension: Adapting medical therapy to hemodynamic response for the prevention of bleeding. *Hepatology* 2002;36:1361-6.
61. Groszmann RJ, Bosch J, Grace ND, et al. Hemodynamic events in a prospective randomized trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. *Gastroenterology* 1990;99:1401-7.
62. Merkel C, Bolognesi M, Sacerdoti D, et al. The hemodynamic response to medical treatment of portal hypertension as a predictor of clinical effectiveness in the primary prophylaxis of variceal bleeding in cirrhosis. *Hepatology* 2000;32:930-4.
63. Thalheimer U, Mela M, Patch D, Burroughs AK. Targeting portal pressure measurements: A critical reappraisal. *Hepatology* 2004;39:286-90.
64. Bosch J, Abraldes JG, Groszmann R. Current management of portal hypertension. *J Hepatol* 2003;38(Suppl 1):S54-S68.
65. Boyer TD. Changing clinical practice with measurements of portal pressure. *Hepatology* 2004;39:283-5.
66. Targownik LE, Spiegel BM, Dulai GS, Karsan HA, Gralnek IM. The cost-effectiveness of hepatic venous pressure gradient monitoring in the prevention of recurrent variceal hemorrhage. *Am J Gastroenterol* 2004;99:1306-15.
67. Chen CY, Sheu MZ, Su SY. Prophylactic endoscopic variceal ligation (EVL) with multiple band ligator for oesophageal varices. *Gastroenterology* 1998;114:A1224. (Abst)
68. Sarin SK, Lamba GS, Kumar M, Misra A, Murthy NS. Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding. *N Engl J Med* 1999;340:988-93.
69. De BK, Ghoshal UC, Das T, Santra A, Biswas PK. Endoscopic variceal ligation for primary prophylaxis of oesophageal variceal bleed: Preliminary report of a randomized controlled trial. *J Gastroenterol Hepatol* 1999;14:220-4.
70. Jutabha R, Jensen DM, Martin P, et al. Initial report of a randomized, prospective study of prophylactic propranolol compared to rubber band ligation for prevention of first variceal hemorrhage in cirrhotics with large esophageal varices. *Gastroenterology* 2000;118:A212. (Abst)
71. de la Mora JG, Farca-Belsaguy AA, Uribe M, de Hoyos-Garza A. Ligation vs. propranolol for primary prophylaxis of variceal bleeding using multiple band ligator and objective measurements of treatment adequacy: Preliminary results. *Gastroenterology* 2000;118:A1434. (Abst)
72. Lui HF, Stanley AJ, Forrest EH, et al. Primary prophylaxis of variceal hemorrhage: A randomized controlled trial comparing band ligation, propranolol, and isosorbide mononitrate. *Gastroenterology* 2002;123:735-44.
73. Lo GH, Chen WC, Chen MH, et al. Endoscopic ligation vs. nadolol in the prevention of first variceal bleeding in patients with cirrhosis. *Gastrointest Endosc* 2004;59:333-8.

74. Schepke M, Kleber G, Nurnberg D, et al. Ligation versus propranolol for the primary prophylaxis of variceal bleeding in cirrhosis. *Hepatology* 2004;40:65-72.
75. Imperiale TF, Chalasani N. A meta-analysis of endoscopic variceal ligation for primary prophylaxis of esophageal variceal bleeding. *Hepatology* 2001;33:802-7.
76. Khuroo MS, Khuroo NS, Farahat KL, Khuroo YS, Sofi AA, Dahab ST. Meta-analysis: Endoscopic variceal ligation for primary prophylaxis of oesophageal variceal bleeding. *Aliment Pharmacol Ther* 2005;21:347-61.
77. Cano I, Urruzuno P, Medina E, et al. Treatment of esophageal varices by endoscopic ligation in children. *Eur J Pediatr Surg* 1995;5:299-302.
78. Celinska-Cedro D, Teisseyre M, Woynarowski M, Socha P, Socha J, Ryzko J. Endoscopic ligation of esophageal varices for prophylaxis of first bleeding in children and adolescents with portal hypertension: Preliminary results of a prospective study. *J Pediatr Surg* 2003;38:1008-11.
79. Reinoso MA, Sharp HL, Rank J. Endoscopic variceal ligation in pediatric patients with portal hypertension secondary to liver cirrhosis. *Gastrointest Endosc* 1997;46:244-6.
80. Sasaki T, Hasegawa T, Nakajima K, et al. Endoscopic variceal ligation in the management of gastroesophageal varices in postoperative biliary atresia. *J Pediatr Surg* 1998;33:1628-32.
81. Sharara AI, Rockey DC. Therapy for primary prophylaxis of varices: And, the winner is...? *Hepatology* 2003;37:473-5.
82. Burroughs AK, Patch D. Primary prevention of bleeding from esophageal varices. *N Engl J Med* 1999;340:1033-5.
83. Garcia-Pagan JC. Non-selective beta-blockers in the prevention of first variceal bleeding. Is there any definite alternative? *J Hepatol* 2002;37:393-5.
84. Spiegel BM, Targownik L, Dulai GS, Karsan HA, Gralnek IM. Endoscopic screening for esophageal varices in cirrhosis: Is it ever cost effective? *Hepatology* 2003;37:366-77.
85. Saab S, DeRosa V, Nieto J, Durazo F, Han S, Roth B. Costs and clinical outcomes of primary prophylaxis of variceal bleeding in patients with hepatic cirrhosis: A decision analytic model. *Am J Gastroenterol* 2003;98:763-70.
86. de Franchis R, Pascal JP, Ancona E, et al. Definitions, methodology and therapeutic strategies in portal hypertension. A consensus development workshop, Baveno, Lake Maggiore, Italy, April 5 and 6, 1990. *J Hepatol* 1992;15:256-61.
87. Jalan R, Hayes PC. UK guidelines on the management of variceal haemorrhage in cirrhotic patients. *British society of gastroenterology. Gut* 2000;46(Suppl 3-4):III1-III15.
88. Grace ND. Diagnosis and treatment of gastrointestinal bleeding secondary to portal hypertension. American college of gastroenterology practice parameters committee. *Am J Gastroenterol* 1997;92:1081-91.
89. Boyer TD. Primary prophylaxis for variceal bleeding: Are we there yet? *Gastroenterology* 2005;128:1120-2.
90. Veatch RM. Doctor does not know best: Why in the new century physicians must stop trying to benefit patients. *J Med Philos* 2000;25:701-21.
91. Howard ER, Stringer MD, Mowat AP. Assessment of injection sclerotherapy in the management of 152 children with oesophageal varices. *Br J Surg* 1988;75:404-8.
92. Maksoud JG, Goncalves ME, Porta G, Miura I, Velhote MC. The endoscopic and surgical management of portal hypertension in children: Analysis of 123 cases. *J Pediatr Surg* 1991;26:178-81.